NEW CONCEPTS IN SEPSIS: BETA BLOCK THE SEPTIC HEART

Dr SA Thula
Inkosi Albert Luthuli Central Hospital
Overview

- Epidemiology
- Pathophysiology of Sepsis
- Pathophysiology of cardiac dysfunction in sepsis
- β-Blockers in the septic heart
- Conclusions
National estimates are generated from the seven-state cohort by using state and national age-specific population estimates from the National Center for Health Statistics and the U.S. Census. The incidence among women was equivalent to that of men 5 years younger. A similar age-based difference was seen in mortality but, in multivariate regression, this difference was explained by underlying comorbidity and site of infection. Published with permission [1].

Current Opinion in Critical Care 2002, 8:465-472
Fig. 1. Pathophysiology of severe sepsis and septic shock. (Adapted from Cinel I, Opal SM. Molecular biology of inflammation and sepsis: a primer. Crit Care Med 2009;37(1):293; with permission.)
Figure 1. The Response to Pathogens, Involving “Cross-Talk” among Many Immune Cells, Including Macrophages, Dendritic Cells, and CD4 T Cells.

Macrophages and dendritic cells are activated by the ingestion of bacteria and by stimulation through cytokines (e.g., interferon-γ) secreted by CD4 T cells. Alternatively, CD4 T cells that have an antiinflammatory profile (type 2 helper T cells [Th2]) secrete interleukin-10, which suppresses macrophage activation. CD4 T cells become activated by stimulation through macrophages or dendritic cells. For example, macrophages and dendritic cells secrete interleukin-12, which activates CD4 T cells to secrete inflammatory (type 1 helper T-cell [Th1]) cytokines. Depending on numerous factors (e.g., the type of organism and the site of infection), macrophages and dendritic cells will respond by inducing either inflammatory or antiinflammatory cytokines or causing a global reduction in cytokine production (anergy). Macrophages or dendritic cells that have previously ingested necrotic cells will induce an inflammatory cytokine profile (Th1). Ingestion of apoptotic cells can induce either an antiinflammatory cytokine profile or anergy. A plus sign indicates up-regulation, and a minus sign indicates down-regulation; in cases where both a plus sign and a minus sign appear, either up-regulation or down-regulation may occur, depending on a variety of factors.
Sepsis and the heart

- Early sepsis $\rightarrow$ ↑catecholamine release $\rightarrow$ ↑energy expenditure

- Later circulatory derangements and mitochondrial dysfunction  tissue hypoxia and dysoxia

- Down regulation of adrenergic receptors and depression of post-receptor signaling pathways
Figure 3. Protocol for early, goal-directed therapy

CVP, central venous pressure; MAP, mean arterial pressure; ScvO2, central venous oxygen saturation. Published with permission [48].

Conventional Thinking
β-Blockers in Sepsis

Normalization of Cellular Metabolism

Decreased cardiac dysfunction

Cytokine Effects

Improved Glucose Homeostasis
<table>
<thead>
<tr>
<th>Model</th>
<th>β-Blocker/Dose/Start</th>
<th>Main Results in β-Blocker-Treated Subjects</th>
<th>Study Limitations/Adverse Events</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal Studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mongrel dogs</td>
<td>Propranolol 0.15 to 1.5 mg/kg, given 5 to 60 mins after endotoxin injection</td>
<td>Survival ↑ from 27% to 72% In vivo: BP ↑, fluid requirements ↓ In vivo: PaO2 ↑ Postmortem: lung injury ↓</td>
<td>Propranolol-treated dogs required infusion of 50% dextrose to prevent hypoglycemia</td>
<td>35</td>
</tr>
<tr>
<td>Endotoxin injection</td>
<td></td>
<td>In vivo: TNFα ↓, lactate = Ex vivo: HR =, SV ↑, CO ↑, cardiac efficiency ↑ Postmortem: β-1 receptor density ↑</td>
<td>Administration of calcium chloride for contractility and atropine for bradycardia</td>
<td></td>
</tr>
<tr>
<td>Wistar rats</td>
<td>Esmolol infusion of 10 mg/kg/hr or 20 mg/kg/hr/s for 24 hrs (in vivo)</td>
<td>In vivo: HR ↓, BP ↓ In vivo: TNFα ↓, IL-6 ↓, HMGB1 ↓, NF-kB activation ↓ Ex vivo: LVEDP ↓, +dP/dt ↓, -dP/dt ↑ Postmortem: lung injury ↓ In vivo: HR ↓, SV =, CO ↓</td>
<td>Esmolol and circulating catecholines excluded from the perfusion medium ex-vivo</td>
<td>38</td>
</tr>
<tr>
<td>Fecal peritonitis</td>
<td></td>
<td>In vivo: HR ↓, BP ↓ In vivo: TNFα ↓, IL-6 ↓, HMGB1 ↓, NF-kB activation ↓ Ex vivo: LVEDP ↓, +dP/dt ↓, -dP/dt ↑</td>
<td>No outcome data</td>
<td></td>
</tr>
<tr>
<td>Isolated perfused heart preparation (ex vivo) 24 hrs after sepsis induction</td>
<td></td>
<td>In vivo: HR ↓, BP ↓ In vivo: TNFα ↓, IL-6 ↓, HMGB1 ↓, NF-kB activation ↓ Ex vivo: LVEDP ↓, +dP/dt ↓, -dP/dt ↑</td>
<td>No outcome data</td>
<td></td>
</tr>
<tr>
<td>Wistar rats</td>
<td>Landiolol infusion of 0.1mg/kg/min for 24 hrs (in vivo)</td>
<td>Landiolol infusion of 0.1mg/kg/min for 24 hrs (in vivo)</td>
<td>Landiolol and circulating catecholines excluded from the perfusion medium ex-vivo</td>
<td>39</td>
</tr>
<tr>
<td>Endotoxin injection</td>
<td></td>
<td>Landiolol infusion of 0.1mg/kg/min for 24 hrs (in vivo) Landiolol infusion of 0.1mg/kg/min for 24 hrs (in vivo)</td>
<td>No outcome data</td>
<td></td>
</tr>
<tr>
<td>Sprague Dawley/Wistar rats</td>
<td>Metoprolol pre- and posttreatment (various doses)</td>
<td>Metoprolol pre- and posttreatment (various doses)</td>
<td>Significant survival benefits only with pre-treatment in endotoxin model</td>
<td>40</td>
</tr>
<tr>
<td>Endotoxin injections/fecal peritonitis</td>
<td></td>
<td>Metoprolol pre- and posttreatment (various doses)</td>
<td>Significant survival benefits only with pre-treatment in endotoxin model</td>
<td></td>
</tr>
<tr>
<td>Patient Studies</td>
<td></td>
<td>Propranolol 5 mg infusion over 2–3 hrs, repeated once after 6–12 hrs</td>
<td>No control group</td>
<td>41</td>
</tr>
<tr>
<td>Septic patients (n = 5) with refractory shock</td>
<td>Esmolol infusion for 3 hrs 6–22 mg/min (goal: HR ↓ 20%)</td>
<td>HR ↓, SV =, CO ↓ Resting energy expenditure = O2 consumption (calorimetry) = ATP concentration in muscle = HR ↓, SV ↑, CO = Overall, NA and milrinone doses ↓ Lactate ↓, CRP ↓ Organ function variables unchanged</td>
<td>Use of antiquated sepsis therapies such as glucagon, high dose steroids, or digitalis</td>
<td></td>
</tr>
<tr>
<td>Mortality 40%</td>
<td>Esmolol infusion for 3 hrs 6–22 mg/min (goal: HR ↓ 20%)</td>
<td>In vivo: HR ↓, BP ↓ In vivo: TNFα ↓, IL-6 ↓, HMGB1 ↓, NF-kB activation ↓ Ex vivo: LVEDP ↓, +dP/dt ↓, -dP/dt ↑</td>
<td>Small study population</td>
<td></td>
</tr>
<tr>
<td>Septic patients (n = 6) without vasopressors</td>
<td></td>
<td>HR ↓, SV =, CO ↓ Resting energy expenditure = O2 consumption (calorimetry) = ATP concentration in muscle = HR ↓, SV ↑, CO = Overall, NA and milrinone doses ↓ Lactate ↓, CRP ↓ Organ function variables unchanged</td>
<td>No control group</td>
<td>42</td>
</tr>
<tr>
<td>Hospital mortality 16%</td>
<td>Esmolol infusion for 3 hrs 6–22 mg/min (goal: HR ↓ 20%)</td>
<td>HR ↓, SV =, CO ↓ Resting energy expenditure = O2 consumption (calorimetry) = ATP concentration in muscle = HR ↓, SV ↑, CO = Overall, NA and milrinone doses ↓ Lactate ↓, CRP ↓ Organ function variables unchanged</td>
<td>Short study population</td>
<td></td>
</tr>
<tr>
<td>Patients with septic shock (n = 40)</td>
<td>Metoprolol via enteral route 47–52 mg/day (goal: HR &lt;95/min) After hemodynamic stabilization Combination with NA, milrinone and vasopressin</td>
<td>Retrospective study No control group NA and milrinone requirements ↑ in 9 and 6 patients, respectively Asymptomatic HR 65/min in 2 patients</td>
<td></td>
<td>43</td>
</tr>
<tr>
<td>SAPS II 53</td>
<td>Metoprolol via enteral route 47–52 mg/day (goal: HR &lt;95/min) After hemodynamic stabilization Combination with NA, milrinone and vasopressin</td>
<td>Retrospective study No control group NA and milrinone requirements ↑ in 9 and 6 patients, respectively Asymptomatic HR 65/min in 2 patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

- Growing body of evidence for reversal of adrenergic stimulation

BUT !!! More Studies